JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 4, 467–478 (1991)

TREATMENT OF ELECTROSTATIC EFFECTS WITHIN THE MOLECULAR MECHANICS METHOD. 3. DOUBLE BONDS AND CONJUGATED SYSTEMS

LJILJANA DOŠEN-MIĆOVIĆ
Department of Chemistry, Faculty of Science, University of Belgrade, 11001 Belgrade, Yugoslavia
SHUSEN LI
Shanghai Institute of Organic Chemistry, 345 Lingling Lu, Shanghai, China
AND
NORMAN L. ALLINGER
Department of Chemistry, University of Georgia, Athens, Georgia 30602, U.S.A.

The previously developed general method (IDME), which includes calculation of electrostatic and solvation effects on conformational equilibria, has been extended to molecules containing double bonds and conjugated systems. It was applied in connection with MM2 studies to the calculation of the charge distributions and dipole moments, and to the conformational energies of some β-substituted cyclohexenes, *exo*-methylenecyclohexanes and benzocycloheptenes. Conformational equilibria and dipole moments were well calculated. It was concluded that electrostatic interactions do not play a major role in determining conformational preferences in these compounds. On the other hand, the energies of the preferred conformations of the ten-membered ring in (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one are poorly calculated without the IDME procedure, and fairly well with it.

INTRODUCTION

Molecular mechanics calculations have been successfully used to study the structures and energies of hydrocarbons and many kinds of monofunctional polar compounds.[1] For molecules containing two or more neighboring polar groups, electrostatic and solvation effects have to be considered in addition, since they significantly affect conformational equilibria. The IDME (induced dipole moment and energy) method[2] has been developed to account for electrostatic effects dealing with charges on a classical level, and considering all inductive interactions between bond dipoles and the bonds themselves. The method may be used to calculate dipole moments, charge distributions and conformational energies in either the vapor phase or in solution. However, only saturated compounds and compounds with isolated carbonyl groups have been considered previously. In order to increase the applicability of the IDME method, we have extended it to molecules containing carbon—carbon double bonds and to some conjugated systems.

BACKGROUND OF THE THEORY

A bond dipole in the IDME method is represented as

$$\boldsymbol{\mu}_{ij} = \boldsymbol{\mu}^{0}_{ij} + \boldsymbol{\mu}^{\mathrm{i}}_{ij} \qquad (1)$$

where $\boldsymbol{\mu}^{0}_{ij}$ is the 'permanent bond dipole' between atoms i and j, $\boldsymbol{\mu}^{\mathrm{i}}_{ij}$ is the bond dipole induced in the i—j bond by all the other non-adjacent bonds in the molecule and $\boldsymbol{\mu}_{ij}$ is the resultant bond dipole moment. The $\boldsymbol{\mu}^{0}_{ij}$ is calculated from IDME parameters.[2]

The induced bond dipole moment ($\boldsymbol{\mu}^{\mathrm{i}}_{ij}$) is given by

$$\boldsymbol{\mu}^{\mathrm{i}}_{ij} = -\boldsymbol{\alpha}_{ij}\mathbf{E}_{kl} - -\boldsymbol{\alpha}_{ij} \sum_{\substack{kl=1 \\ kl \neq ij}}^{N} \mathbf{T}_{ij,kl}\boldsymbol{\mu}_{kl} \qquad (2)$$

where $\boldsymbol{\alpha}_{ij}$ is the bond polarizability tensor which contains three components, longitudinal, transverse and vertical bond polarizabilities, available in the literature,[3] and $\mathbf{T}_{ij,kl}$ is the dipole field tensor.

After each μ_{ij} has been calculated, the net charge on

0894–3230/91/080467–12$06.00

Revised December 1990

atom i (q_i) is calculated from

$$q_i = \sum_j \theta^j{}_i \qquad \theta^j{}_i = \mu^1{}_{ij}/R_{ij} \tag{3}$$

where $\theta^j{}_i$ is the net charge on atom i due to the polarization of the bond $i{-}j$, R_{ij} is the bond length and $\mu^1{}_{ij}$ is the longitudinal component of the $i{-}j$ bond dipole moment.

The charge interaction energy is given by

$$E_{\mathrm{ch}} = \sum_{\substack{i=1 \\ j>i}}^{n-1} q_i q_j / \varepsilon R_{ij} \tag{4}$$

where ε is the dielectric constant between interacting charges and R_{ij} is the interatomic distance.

Therefore, the conformational energy in the vapor (E^{v}) is given by

$$E^{\mathrm{v}} = E_{\mathrm{st}}^{\mathrm{MM2}} - E_{\mathrm{dipole}}^{\mathrm{MM2}} + E_{\mathrm{ch}} \tag{5}$$

where $E_{\mathrm{st}}^{\mathrm{MM2}}$ is the steric energy of a conformer as given by the MM2 (or MMP2) program (i.e. including dipole–dipole interaction energy) and $E_{\mathrm{dipole}}^{\mathrm{MM2}}$ is the dipole interaction energy.

The conformational energy difference is given by

$$\Delta E^{\mathrm{v}} = \Delta E_{\mathrm{st}}^{\mathrm{MM2}} - \Delta E_{\mathrm{dipole}}^{\mathrm{MM2}} + \Delta E_{\mathrm{ch}}$$

The generally accepted assumption is made that for the gas phase $\Delta H = \Delta E$, and that the contributions to ΔS except for the entropy of mixing are negligible. Therefore, $\Delta G^{\mathrm{v}} = \Delta H - T\Delta S_{\mathrm{mix}}$. The solvation energy calculations, included in the IDME program, are based on the reaction field theory and they give the difference between the conformational free energy in the vapor (ΔG^{v}) and in solution (ΔG^{s}):

$$SE = \Delta G^{\mathrm{v}} - \Delta G^{\mathrm{s}} \tag{6}$$

$$\Delta G^{\mathrm{s}} = \Delta G^{\mathrm{v}} - SE \tag{7}$$

From equation (7), the conformational free energy difference in solution (ΔG^{s}) can be calculated and used to compare the solvation effects of different solvents.

The double bond carbon (C_{sp^2}, type 2 in MM2 and MM3) is treated in this work as a new atom type. Therefore, there are three new bonds in non-conjugated compounds: the C=C double bond, the $C_{sp^3}{-}C_{sp^2}$ single bond and the $C_{sp^2}{-}H$ single bond. The following parameters have to be determined; $\delta^0_{(2)}$, $\nu_{(2,2)}$, $\gamma_{2(2)}$, $\nu_{(1,2)}$, $\gamma_{2(1)}$, $\gamma_{1(2)}$, $\nu_{(2,5)}$, $\gamma_{2(5)}$, and $\gamma_{5(2)}$, where C_{sp^2} is the atom type 2, C_{sp^3} is the atom type 1 and H is the atom type 5. The group of parameters [$\delta^0_{(i)}$, $\gamma_{i(j)}$, $\nu_{(ij)}$] is defined for each atom type or the bond type in the molecule, based on Del Re MO–LCAO considerations.[4] The parameters are related through the following equations:

$$\delta_i = \delta_i^0 + \sum_{j \text{ adj. to } i} \gamma_{i(j)} \delta_j$$

$$Q_{ij} = (\delta_j - \delta_i)/\nu_{ij}$$

$$\mu_{ij}^0 = Q_{ij} R_j$$

The value of $\delta^0_{(i)}$ depends only on the nature of atoms i, and it is proportional to its electronegativity. The value of $\gamma_{i(j)}$ depends on atom i and each adjacent atom j and represents the polarizability of atom i on the part of atom j. The parameter $\nu_{(ij)}$ depends only on the nature of bond $i{-}j$. The originally chosen parameters have been adjusted to reproduce the experimentally determined dipole moments and charge distributions in some simple molecules. The μ^0_{ij} value was calculated from the bond charge Q_{ij} and the bond length R_{ij}.

The polarizabilities of the C=C bond are available in the literature[3] and those of the $C_{sp^2}{-}C_{sp^3}$ and $C_{sp^2}{-}H$ bonds are taken to be the same as the $C_{sp^3}{-}C_{sp^3}$ and $C_{sp^3}{-}H$ single bonds, respectively. The difference in bond refractions between the $C_{sp^2}{-}C_{sp^3}$ and the $C_{sp^3}{-}C_{sp^3}$ bonds is small.[3] Consequently, the difference in bond polarizabilities, which is proportional to the bond refraction difference, also is small. This difference was estimated to be *ca* $0{\cdot}1 \times 10^{-24}\,\mathrm{cm}^3$. Taking into account the small absolute values for the C=C and the C—H bonds, this would cause a negligible difference in calculated, induced bond moments.

In the case of non-conjugated alkenes, the only requirement is to choose values for the above new parameters to make the μ_{calc} as close to μ_{exp} as possible for a group of compounds. The parameters for the C_{sp^2} atom type, and the corresponding bond parameters originally taken as equal to those of the C_{sp^3} atom type, were then modified by comparison of the calculated with the observed molecular dipole moments.

The main difference between the $C_{sp^2}{-}C_{sp^2}$ bonds in conjugated and non-conjugated systems is the bond order. There are two parameters related to the bond order: the resonance parameter (ν_{ij}) and the polarizability (α_{ij}). Since ν_{ij} is assumed to be independent of the surroundings in the IDME method, $\nu(2, 2)$ is considered to be independent of the bond order in the present IDME version.

The polarizabilities of the conjugated $C_{sp^2}{-}C_{sp^2}$ bonds are given by

$$\alpha_{2-2}^{\mathrm{con}} = \alpha_{1-1} + (\alpha_{2-2}^{\mathrm{non}} - \alpha_{1-1})BC \tag{8}$$

where $\alpha_{2-2}^{\mathrm{con}}$ is the polarizability of the $C^i_{sp^2}{-}C^j_{sp^2}$ bond, α_{1-1} is the polarizability of the C—C single bond and $\alpha_{2-2}^{\mathrm{non}}$ is the polarizability of the C=C bond in non-conjugated system. B is the bond order of the $C^i_{sp^2}{-}C^j_{sp^2}$ bond (which is calculated by SCF calculations in MMP2) and C is the proportionality constant estimated by equation (9).

Generally, benzene can be treated as a Kekulé form consisting of three double bonds and three single bonds, and the bond order of the $C_{sp^2}-C_{sp^2}$ bond in benzene is 0·6667. Therefore, the polarizability of the $C_{sp^2}-C_{sp^2}$ bond in benzene (α^{b}_{2-2}) is

$$\alpha^{b}_{2-2} = (3\alpha^{non}_{2-2} + 3\alpha_{1-1})/6 = \alpha_{1-1} + (\alpha^{non}_{2-2} - \alpha_{1-1}) \times 0{\cdot}6667C \quad (9)$$

and

$$C = [(3\alpha^{non}_{2-2} + 3\alpha_{1-1})/6 - \alpha_{1-1}]/[0{\cdot}6667(\alpha^{non}_{2-2} - \alpha_{1-1})] = 0{\cdot}74996$$

RESULTS AND DISCUSSION

All the new parameters from the above treatment which are related to the C_{sp^2} carbon (atom type 2) are listed in Table 1. The calculated dipole moments of the molecules containing non-conjugated and conjugated C=C double bonds are presented in Table 2. The agreement with the experimental values has an average deviation of 0·11 D.

Table 1. The IDME parameters

Parameter	Bond ($i-j$) $C_{sp^2}-C_{sp^3}$	$C_{sp^2}-C_{sp^2}$	$C_{sp^2}-H$
δ_i^0	0·30	0·30	0·30
δ_j^0	0·07	0·30	0·00
ν_{ij}	2·0	2·0	3·0
$\gamma_{i(j)}$	0·1	0·1	0·6
$\gamma_{j(i)}$	0·1	0·1	0·3
Lp[a]	0·99	2·80	0·64
Tp[a]	0·27	0·73	0·64
Vp[a]	0·27	0·77	0·64
$CR_{(i)}$[b]	0·771	0·771	0·771
$CR_{(j)}$	0·771	0·771	0·30

[a] Lp, Tp and Vp are longitudinal, transverse and vertical bond polarizabilities, respectively (in 10^{-24} cm^3).

[b] $CR_{(i)}$ is the covalent radius of atom i.

With aliphatic compounds,[2] the charge distributions calculated by IDME are similar to those obtained by *ab initio* (STO-3G) calculations.[6] The molecules propene and toluene, for instance, have electric dipole moments as a result of interaction of a methyl group with the unsaturated system. Replacement of a hydrogen in ethylene with a methyl group leads to a redistribution of charge, making the β-carbon of the vinyl group more negative (Figure 1). Similar features are found in toluene where carbons at the *ortho* and *para* positions

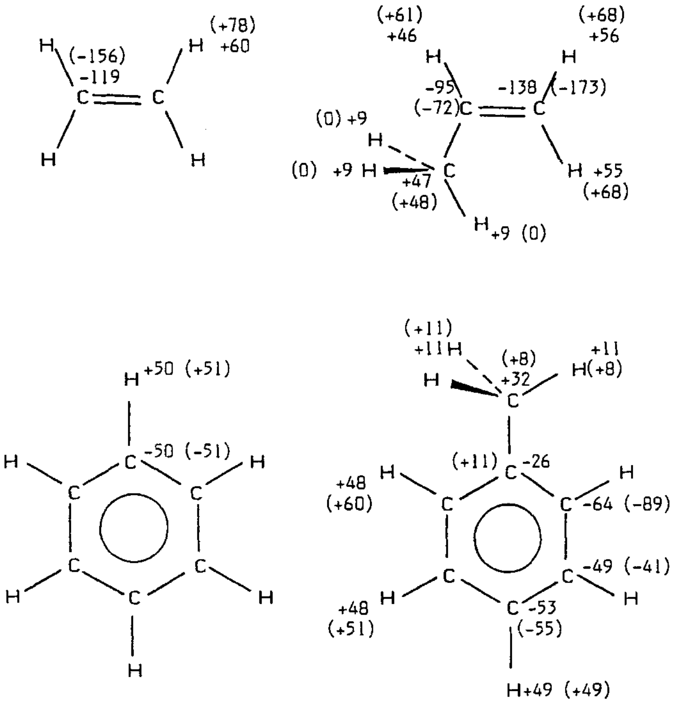

Figure 1. Change distribution (10^{-3} electron) calculated by the IDME method and by the *ab initio* (STO-3G)[6] method (in parentheses)

Table 2. Dipole moments (D)

Compound	Conformation	μ_{exp}[a]	μ_{calc}	μ_{MM2}
Propene		0·35	0·40	0·30
gauche-3-Fluoropropene		1·94	1·85	1·74
cis-3-Fluoropropene		1·77	1·61	1·73
3-Chloropropene		1·9–2·04	1·81[b]	1·85[b]
But-1-ene		0·36–0·44	0·43	0·30
3-Chlorobut-1-ene		1·99[c]	1·91[b]	1·86[b]
1-Chlorobut-2-ene		2·01, 2·10[c]	2·19	1·94
3-Methylbut-1-ene		0·25	0·42	0·30
Cyclohexene		0·61	0·46	0·50
Methylenecyclohexane			0·50	0·32
2-Methylbuta-1,3-diene		0·26	0·40[b]	0·30
Toluene		0·38	0·46	0·30
1,2-Dimethylbenzene		0·62	0·70	0·51
Benzal dichloride		2·05–2·07[c]	2·22	2·00
Benzotrichloride		2·04–2·17[c]	2·21	1·69
Benzyl fluoride		1·77[c]	1·74	1·73
Benzotrifluoride		2·86, 2·54–2·61[c]	2·57	2·56
4-Chlorocyclohexene	a		1·86	
	e		1·78	
4-Bromocyclohexene	a		1·91	
	e		1·83	
1,2-Dimethyl-4-chlorocyclohexene	a		1·97	
	e		2·66	
4-Chlorobenzocycloheptene	a		2·09	
	e		1·86	
4-Methoxycyclohexene	ag1		1·54	
	ag2		1·29	
	aa		1·09	
	eg1		1·35	
	eg2		1·02	
	ea		1·29	
3-Methoxy-1-methylenecyclohexane	ag1		1·15	
	ag2		1·61	
	aa		1·39	
	eg1		0·84	
	eg2		1·41	
	ea		1·50	
3-Methoxy-1-(isopropylidene)cyclohexane	ag1		1·09	
	ag2		1·13	
	aa		1·48	
	eg1		1·33	
	eg2		1·31	
	ea		1·42	
4-Methoxybenzocycloheptene	ag1		1·35	
	ag2		1·88	
	aa		1·43	
	eg1		0·66	
	eg2		1·41	
	ea		1·59	
4-Hydroxycyclohexene	ag1		1·82	
	ag2		1·52	
	aa		1·40	
	eg1		1·64	
	eg2		1·29	
	ea		1·51	
3-Hydroxy-1-methylenecyclohexene	ag1		1·42	
	ag2		1·90	
	aa		1·70	

(*continued*)

Table 2. (*continued*)

Compound	Conformation	μ_{exp}[a]	μ_{calc}	μ_{MM2}
	eg1		1·10	
	eg2		1·69	
	ea		1·76	
4-Hydroxybenzocycloheptene	ag1		1·46	
	ag2		2·18	
	aa		1·67	
	eg1		0·85	
	eg2		1·72	
	ea		1·79	
4-Phenylcyclohexanone	a		2·87	
	e		2·77	
4-Methyl-4-phenylcyclohexanone	aΦ		3·03	
	eΦ		2·88	
r-1-Chloro-1-methyl-*t*-4-phenylcyclohexane	aΦ		1·60	
	eΦ		1·79	
r-1-Fluoro-1-methyl-*t*-4-phenylcyclohexane	aΦ		1·43	
	eΦ		1·65	
1-Methyl-1-phenylcyclohexane	aΦ		0·45	
	eΦ		0·52	
5-Methyl-5-phenyl-1,3-dioxane	aΦ		2·16	
	eΦ		1·72	

[a] Experimental values are taken from Ref. 5.

[b] Dipole moments are weighed averages wherever more than one conformation contributes.

[c] These values in benzene, the others in the gas phase.

are more negative than those at the *meta* position. In *o*-xylene the charge distribution (in 10^{-3} electron) was calculated to be $C_{1,2} = -40$, $C_{3,6} = -62$ and $C_{4,5} = -52$.

The procedure followed in the conformational energy calculations is described in the preceding section. The solvent effects on the conformational energies were obtained from the reaction field theory[2,7] using the model of a spherical cavity with the sphere centered at the center of the charge of the molecule.

Unfortunately, there are no systematic studies on the conformational effects of the double bond, and experimental data are scarce. The available experimental data for substituted cyclohexene, *exo*-methylenecyclohexane and benzocycloheptene are given in Table 4, together with the calculated values. The calculations are limited to alkyl, Cl, Br, OR and OH groups by the currently available IDME parameters. The use of non-spherical charge distributions around the ether oxygen provided[2b] better results earlier in the case of substituted 1,3-dioxanes. Therefore, C—O and O—lone pair (lp) dipoles were taken from the MM2 program and their bond polarizabilities are as in Ref. 2. The torsional constants for the $C_{sp^2}—C_{sp^3}—C_{sp^3}—X$ dihedral angles (where X = Cl, Br, O) are either unknown or they are not definitive. The one-fold (V_1) or two-fold (V_2) torsional constants were estimated and their values are presented in Table 3. The available data show that adjustment of the V_2 term is the best way to duplicate the axial–equatorial ratios of the chloro and bromo compounds. In the case of oxygen-containing compounds, adjustment of the V_1 term for the 2—1—1—6 ($C_{sp^2}—C_{sp^3}—C_{sp^3}—O$) dihedral angle provided better agreement of the calculated conformational energies with the experimental results.

Table 3. Torsional constants[a]
Angle: $C_{sp^2}—C_{sp^3}—C_{sp^3}—X$ (2—1—1—X).

X	V_1	V_2	V_3
O	0·8	0·0	0·18
F	0·0	−0·10	0·0
Cl	0·0	−0·35	0·0
Br	0·0	−0·50	0·0

[a] For the angle $(O=)C_{sp^2}—C_{sp^3}—C_{sp^3}—X$ (3—1—1—X) $V_1 = V_2 = V_3 = 0·0$ when X = Cl, Br, O, F.

Table 4 compares the calculated and experimental values of conformational energies. Both calculations and experiment indicate that the axial methyl group ($X = CH_3$) in 4-X-cyclohexene, 3-X-methylenecyclohexene and 4-X-benzocycloheptene (see Figure 6) encounters smaller repulsive interactions than in the corresponding cyclohexane, and the amount of equatorial conformer is reduced. Electrostatic intramolecular interactions and the solvent effect on the conformational equilibria were calculated to be negli-

Table 4. Conformational energies kcal mol^{-1}

				ΔG		
No.	Compound	Solvent	ε[a]	ΔG^n	ΔG^n_{MM2}	Experimental
1	4-Methylcyclohexene	Gas	1·5	1·43		
		C_8H_{18}	2·0	1·43	1·42	1·45[i], 1·15[j]
2	3-Methyl-1-methylenecyclohexane	Gas	1·5	1·32	1·32	
		CF_2Cl_2	2·13	1·32	1·32	0·82[b]
		$CHFCl_2$	5·34	1·32	1·32	0·71
3	4-Methylbenzocycloheptene	Gas	1·5	0·65	0·64	
		CS_2	2·6	0·65	0·64	0·91[c]
		$CHFCl_2$	5·34	0·66	0·64	0·88
4	4-Chlorocyclohexene	Gas	1·5	0·53	0·50	
		CF_2Cl_2	2·13	0·53	0·47	0·31[f]
		CHF_2Cl	6·11	0·52	0·43	−0·02 (0·20)[d]
5	1,2-Dimethyl-4-chlorocyclohexene	Gas	1·5	0·47	0·53	
		CF_2Cl_2	2·13	0·48	0·49	0·38[f]
		$CHFCl_2$	5·34	0·49	0·42	0·06
6	4-Bromocyclohexene	Gas	1·5	0·42	0·52	
		CF_2Cl_2	2·13	0·42	0·50	0·27[f]
7	4-Chlorobenzocycloheptene	Gas	1·5	0·49	0·09	
		CS_2	2·6	0·49	−0·01	0·70[c]
		$CHFCl_2$	5·34	0·49	−0·07	0·24
8	4-Methoxycyclohexene	Gas	1·5	0·80	0·52	
		C_6H_{12}	2·0	0·80	0·50	0·53 ± 0·2[g]
9	3-Methoxy-1-methylenecyclohexane	Gas	1·5	0·63	0·38	
		CF_2Cl_2	2·13	0·63	0·32	0·80[h]
		$CHFCl_2$	5·34	0·63	0·26	0·11
10	3-Methoxy-1-(isopropylidene)cyclohexane	Gas	1·5	0·37	0·13	
		CF_2Cl_2	2·13	0·37	0·04	0·19[h]
		$CHFCl_2$	5·34	0·37	0·01	0·08
11	4-Methoxybenzocycloheptene	Gas	1·5	−0·03	−0·39	
		CS_2	2·13	−0·05	−0·47	0·43[c]
		$CHFCl_2$	5·34	−0·08	−0·59	0·26
12	4-Hydroxycyclohexene	Gas	1·5	0·90	0·41	
		C_6D_{12}	2·0	0·90	0·39	0·47[g]
		CF_2Cl_2	2·13	0·90	0·39	0·22[f]
13	1,2-Dimethyl-4-hydroxycyclohexene	Gas	1·5	0·77	0·57	
		CF_2Cl_2	2·13	0·77	0·50	0·70[f]
14	3-Hydroxy-1-methylenecyclohexane	Gas	1·5	0·83	0·40	
		CF_2Cl_2	2·13	0·83	0·36	1·12[b]
		$CHFCl_2$	5·34	0·83	0·30	0·71
15	4-Hydroxybenzocycloheptene	Gas	1·5	0·81	0·40	
		CF^2Cl_2	2·13	0·79	0·34	
		$CHFCl_2$	5·34	0·78	0·26	1·20[c,e]
16	4-Phenylcyclohexanone	Gas	1·5	2·30[k]		
		Et_2O	4·22	2·25		
		$(CH_3)_2O$	20·7	2·23		
17	4-Methyl-4-phenylcyclohexanone	Gas	1·5	−0·56[k]		
		Et_2O	4·22	−0·59		
		$(CH_3)_2O$	20·7	−0·62		
18	*r*-1-Chloro-1-methyl-*t*-4-phenylcyclohexane	Gas	1·5	1·43[k]		
		$CFCl_3$	2·3	1·49		
		Et_2O	4·22	1·57		
		$(CH_3)_2O$	20·7	1·74		
19	*r*-1-Fluoro-1-methyl-*t*-4-phenylcyclohexane	Gas	1·5	1·07[k]		
		$CFCl_3$	2·3	1·13		
		ET_2O	4·22	1·23		
		$(CH_3)_2O$	20·7	1·40		

(*continued*)

Table 4. (*continued*)

No.	Compound	Solvent	ε[a]	ΔG^{n}	$\Delta G^{n}_{\mathrm{MM2}}$	Experimental
			ΔG			
20	1-Methyl-1-phenylcyclohexane	Gas	1·5	−0·25[k]	−0·25	
		$CFCl_3$	2·3	−0·25	−0·25	−0·37[l]
		Et_2O	4·22	−0·25	−0·25	
21	5-Methyl-5-phenyl-1-1,3-dioxane	Gas	1·5	0·97[k]	0·12	
		$CFCl_3$	2·3	0·91	0·06	0·45[l]
		Et_2O	4·22	0·92	0·00	0·54[m]

[a] Dielectric constant.
[b] Ref. 8.
[c] Ref. 9.
[d] In $CD_2{=}CDCl$.
[e] In tetrahydrofuran.
[f] Ref. 10.
[g] Ref. 11, not affected by the change in solvent polarity.
[h] Ref. 12.
[i] Ref. 13, ΔH_{a-e}
[j] Ref. 13.
[k] $\Delta G_{\Phi(a)-\Phi(e)}$.
[l] Ref. 14.
[m] Ref. 15.
[n] The 2-1-1-X type (X = Cl, Br) torsional constants set as $V_1 = V_2 = V_3 = 0{\cdot}0$.

gible for all three series of compounds when $X = CH_3$, and also for 3-methylcyclohexanone (Table 5).

The stabilization of the β-axial conformation is not as important for the heteroatom-substituted systems as it is for the methyl-substituted compounds. According to the IDME calculations, the axial conformations of compounds **4**–**7** are actually destabilized by the electrostatic interactions by 0·41, 0·41, 0·49, and 0·79 kcal mol^{-1} (1 kcal = 4·184 kJ), respectively. The calculated energy of the axial form is higher than that found experimen-

Table 5. Conformational energies (kcal mol^{-1})(a − e)

Compound	ΔE_{st}[a]	ΔE_{ch}	Gas phase	Solution	Experimental[b,c]
			ΔG		
2,2,3-Trimethylcyclohexanone	0·93	0·02	0·95	0·97	0·90
3-Methylcyclohexanone	1·37	0·00	1·37	1·38	
2,2,5-Trimethylcyclohexanone	1·41	0·00	1·41	1·43	1·07
2,2-Dimethyl-3-bromocyclohexanone	1·15	−0·03	1·12	1·12	0·94
2,2-Dimethyl-3-chlorocyclohexanone	0·86	−0·17	0·69	0·68	0·53
2,2-Dimethyl-3methoxycyclohexanone[d]	0·47	−0·95	−0·45	−0·41	−0·02
2,2-Dimethyl-3-fluorocyclohexanone	0·39	−0·69	−0·39	−0·36	−0·59
3-Methyl-1-methylenecyclohexane	1·32	0·01	1·33	1·33	0·82
3-Methyl-1-(isopropylidene)cyclohexane	0·96	0·01	0·97	0·97	
3-Bromo-1-methylenecyclohexane	−0·10	0·57	0·47	0·51[e]	
3-Chloro-1-methylenecyclohexane	−0·12	0·57	0·45	0·50[e]	
3-Methoxy-1-methylenecyclohexane	0·74	−0·10	0·63	0·63[f]	0·80
3-Fluoro-1-methylenecyclohexane	−0·02	0·61	0·59	0·65[e] 0·72[g]	

[a] The 3—1—1—X torsional constants are $V_1 = V_2 = V_3 = 0{\cdot}0$.
[b] In $CDCl_3$ solution, $\varepsilon = 4{\cdot}8$.
[c] Ref. 16.
[d] Conformations ag2 and eg2 were considered for this compound; conformations ag1 and eg1 are not energy minima and aa and ea have conformational energies higher than 2·0 kcal mol^{-1}.
[e] In Et_2O, $\varepsilon = 4{\cdot}22$.
[f] In CF_2Cl_2, $\varepsilon = 2{\cdot}13$
[g] In acetone, $\varepsilon = 20{\cdot}7$.

tally. However, orbital interactions would also have an important bearing on the conformational equilibria in question. The donation of electron density into the π^*_{CC} orbital by a β-axial substituent is expected to be more effective in the case of second-row and larger atoms (Cl, Br) than in the case of the oxygen. This stabilizing effect for the β-axial substituent is introduced in the MM2 calculations through the negative value of the two-fold torsional constant of the $C_{sp^2}—C_{sp^3}—C_{sp^3}—Cl$ (Br), which brings the calculated values of the conformational energies into good agreement with the experimentally determined values.

In 4-phenylcyclohexanone (**16**) the phenyl group is far from the C=O group and their non-bonded orbital interactions are negligible. Only 2% of the axial form was calculated to exist in the conformational mixture. The electrostatic interactions stabilize the axial conformation by 0·25 kcal mol^{-1} (a shift of about 1% toward axial). This is insufficient to counterbalance the steric destabilization and to provide the axial form in a detectable amount. The 4-Methyl-4-phenylcyclohexanone (**17**) has a measurable conformational equilibrium. The vapor-phase conformational free energy is $\Delta G(\mathrm{a}\Phi - \mathrm{e}\Phi) = -0{\cdot}56$ kcal mol^{-1} compared with $-0{\cdot}25$ kcal mol^{-1} in 1-methyl-1-phenylcyclohexane. The axial conformation of the phenyl group is calculated to be stabilized by electrostatic interactions of 0·3 kcal mol^{-1}. This is small compared with the corresponding value in 4-chlorocyclohexanone,[2] 1·01 kcal mol^{-1}, but reasonable considering the weaker polarity of the phenyl group compared with the chlorine. Polar solvents lead to the further stabilization of the axial form (Table 4).

Next we examined the *r*-1-halo-1-methyl-*t*-4-phenylcyclohexanes[18,19] (Table 4). In these compounds the conformation with axial phenyl is stabilized by electrostatic interactions (0·25 kcal mol^{-1}). The solvent effects are not negligible, but the dipole and quadrupole terms act in the opposite direction, stabilizing the equatorial phenyl conformation, owing to its higher quadrupole moment (Table 4).

The oxygen-containing compounds (**8**–**15**) have been the subject of several investigations.[8-12,17] Lambert and Taba found[12] that in a non-polar solvent (CF_2Cl_2) the equatorial isomer of the 3-methoxy-*exo*-methylenecyclohexane is favored over the axial isomer. Destabilization of the axial form is claimed[12,17] to be due to dipole–dipole (CH_3O–double bond) interactions. The large increase in axial conformation in polar solvent ($CHFCl_2$) tends to support this conclusion. However, a similar solvent effect was observed for methoxycyclohexane and cyclohexanol. It therefore seems that the CH_3O–double bond interactions have little influence on solvent effects in this system. The other effect which seemed to support the idea that the axial conformation of **9** is destabilized by dipole–dipole interactions is the decrease of the equatorial preference of CH_3O (from 0·80 to 0·19 kcal mol^{-1}) when the *exo*-methylene group ($C{=}CH_2$) was replaced with isopropylidene ($C{=}CMe_2$), the high electrical symmetry of which gives a negligible dipole. The MM2 calculations reveal, however, that this decrease of the equatorial preference on going from **9** to **10** is a consequence of the stabilization of the axial form of **10** by steric interactions. This stabilization is due mainly to the van der Waals interactions other than 1,4. The electrostatic interactions for compounds **8**–**15** are calculated to be small ($\Delta E_{ch} = 0{\cdot}1$ kcal mol^{-1} or lower), and the major factor in the stabilization of the equatorial form is believed to be through bond–orbital interactions.[16,17] The three possible rotamers have been considered for each conformation of **8**–**15**, as represented in Figure 2 for the case of 4-OR-cyclohexene ($R = H, CH_3$). The calculated free energy differences are in reasonable agreement with experimental values determined in solvents of low polarity.

The calculated solvent effects on the conformational equilibria are small (Table 4), mainly because the dipole and quadrupole terms are small and of about equal magnitude for all the conformers of a given compound. It has been found earlier[18] that the octupole and higher order terms contribute to the solvation energy of isomers of dichloroethylene[18] and to the solvent effect on amine basicities.[19] Similarly to the procedure described[19] earlier, we developed equation 10, based on the reaction field theory, for the calculation of the solvent effect on conformational equilibria which includes terms higher then quadrupole:

$$w = \frac{1}{2}\sum_{l=0}^{\infty}\frac{(l+1)(\varepsilon_0-\varepsilon)}{\varepsilon_0(\varepsilon_0 l+\varepsilon(l+1))}\sum_{ij}\frac{q_i q_j r_i^l r_j^l}{a^{2l+1}}P_l(r_i r_j) \qquad (10)$$

where w is the work required to bring the system of charges ($q_i, i = 1, N$) from infinity to the point described by position vectors (r_i) within the cavity of radius a, in a dielectric; $\varepsilon, \varepsilon_0$ are dielectric constants outside and inside the cavity, respectively and $P_l(r_i r_j)$ is a Legendre polynomial of order l, where $l = 1$ represents dipole, $l = 2$ quadrupole, and so on. Although many terms were included to obtain convergence, the difference in every particular term between axial and equatorial conformers is small, and the overall calculated solvent effect on the conformational equilibria is negligible. Some other efforts have been made to change the charge distribution of the double bond through the introduction of a π-electron dipole perpendicular to the plane of the double bond, or through the change in magnitude of the bond polarizability components of the $C_{sp^2}—C_{sp^2}$ and $C_{sp^2}—C_{sp^3}$ bonds. None of these changes produced any noticeable effect in the calculated solvation energies.

In compounds **20** and **21**, the equatorial phenyl group has three stable conformations (Figure 3) $\mathrm{e}\Phi\|$, $\mathrm{e}\Phi\perp$

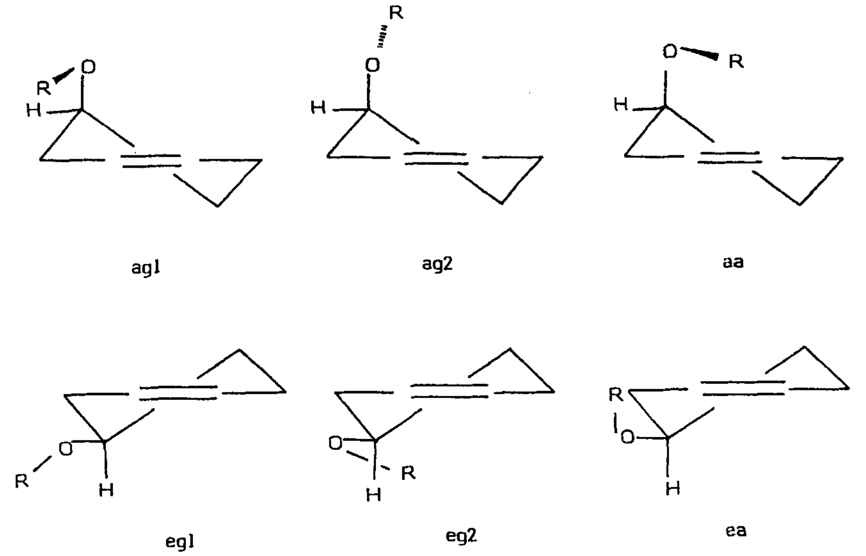

Figure 2. Six conformations considered for 4-OR-cyclohexene (R = H, CH_3)

and eΦ, while the axial phenyl group has two conformations, aΦ|| and aΦ⊥ for **20** and aΦ|| and aΦ for **21**. The eΦ conformation is the most stable of the equatorial phenyl conformations in both **20** and **21**, and it is further stabilized by the entropy of mixing (*dl* pair). In compound **20**, the charge energy difference between the conformers is negligible, whereas in **21** the charge energies are 1·31, 1·59, 1·51, 0·0 and 1·45 kcal mol^{-1} for the conformations eΦ||, eΦ⊥, eΦ, aΦ|| and aΦ, respectively. Stabilization of the aΦ|| conformation of **21** by charge interactions is counterbalanced by the more important steric interactions, so that the aΦ|| conformation does not contribute to the conformational mixture of **21**. In contrast to **20**, where aΦ⊥ is the most stable of all the conformations, this conformation does not correspond to an energy minimum in **21**, where aΦ is the sole conformation of the axial phenyl group and eΦ is the global minimum energy conformation. The

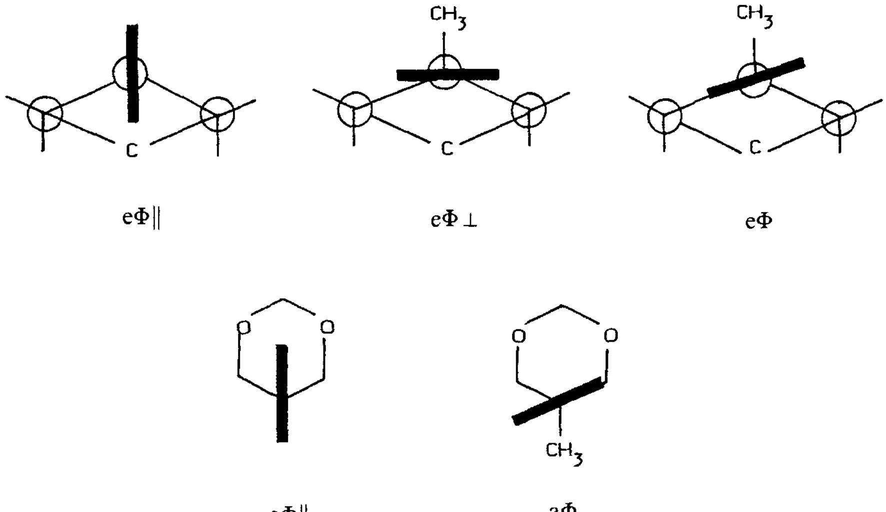

Figure 3. Five conformations considered for 5-methyl-5-phenyl-1,3-dioxane

solvent effect on the conformational distribution in **20** is negligible, whereas for 21 it stabilizes the axial phenyl conformations slightly.

In Table 4 is summarized the conformational energy information obtained by the MM2 and MM2–IDME methods. There is generally little difference between the two groups of results. The MM2–IDME method gives a lower average deviation of 0·34 kcal mol^{-1} compared with 0·41 kcal mol^{-1} obtained by MM2. The results of this type of calculation are considered to be in good agreement with the experimental results if the average deviation is up to 0·2 kcal mol^{-1}, whereas the agreement is considered to be fair when the average deviation is between *ca* 0·2 and 0·4 kcal mol^{-1}. The maximum deviation (0·68 kcal mol^{-1} in MM2–IDME compared with 0·69 kcal mol^{-1} in MM2) refers to an oxygen-containing compound where conformational[16,17] and solvation changes are believed to be due to effects other than the electrostatic effects treated here. The NMR results,[11] obtained in ten solvents with dielectric constants ranging from 2 to 49, for **8** and **12**, for instance, reveal that there is no systematic variation of ΔG with solvent polarity.

Therefore, it appears that electrostatic interactions, including interactions of the atomic charges arising from through-bond and through-space inductive effects between the double bond and the polar substituents, do not play a major role in determining the positions of these conformational equilibria, nor does the solvent effect. The observed solvent effects are probably due to specific interactions with the solvent, not accounted for in the IDME model. In contrast, the conformational equilibria in 2,2-dimethyl-3-X-cyclohexanones ($X = Br, Cl, OCH_3, F$) (Table 5), where two strongly polar bonds are interacting, depends on the electronegativity of the X substituent. This dependence is properly calculated by the IDME method.

The calculated and experimental values of the conformational energies for 2,2-dimethyl-3-X-cyclohexanones and 3-X-1-methylenecyclohexane are compared in Table 5. While the variation in ΔE_{ch} is small on going from bomine to fluorine in 3-X-1-methylenecyclohexane, owing to the small dipole of the C=C bond, the charge interaction energy ΔE_{ch} works to stabilize the axial conformation of 2,2-dimethyl-3-X-cyclohexanone. Its magnitude in this series of compounds increases with β-substituent electronegativity and is the major factor leading to the stabilization of the axial fluorine compared with the predominantly equatorial bromine in the 2,2-dimethyl-3-X-cyclohexanones.

In a paper by Bowen and Allinger,[20] these electrostatic interactions were incorporated in the MM2 calculations through the one-fold torsional term of the $(O{=})C_{sp^2}{-}C_{sp^3}{-}C_{sp^3}{-}X$ (3—1—1—X) dihedral angle. The solvent effect is calculated to be small for these compounds, although dipole and quadrupole terms are both important, but they are opposite in sign, and almost cancel each other.

An example illustrating how the charge distribution of a double bond affects conformational energies is the conformational distribution of a ten-membered ring in (*E*)-3β-acetoxy-5-,10-seco-1(10)-cholesten-5-one (**22**) (Figure 4). It has been found experimentally[21] that A1 is the major conformation in solution (86%), with 14% of the minor conformation B2. The MM2(85) force

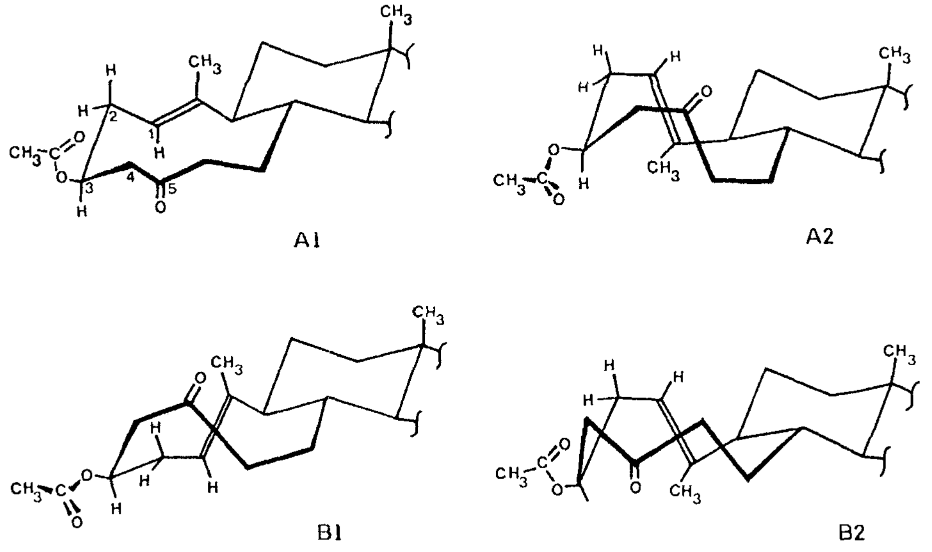

Figure 4. Four stable conformations of (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one (**22**)

Table 6. Conformational energies of **22** (kcal mol^{-1})

Method		A1	A2	B1	B2
MM2(85)	Gas phase	1·52	0·0	4·16	2·08
		7%	90%	0%	3%
MM2(87)[a]	Gas phase	0·74	0·0	4·09	1·22
		20%	71%	0%	9%
	$CHCl_3$, $\varepsilon = 4·8$	0·78	0·0	4·11	1·37
		19%	72%	0%	9%
MM2(87)[a] + IDME[b]	Gas phase	0·34	0·0	3·77	0·98
		32%	57%	0%	11%
MM2(87)[a] + IDME[b]	$CHCl_3$	0·0	1·86	3·70	2·03
		93%	4%	0%	3%
Experimental[c]	$CHCl_3$	86%	—	—	14%

[a] Torsional parameters from Ref. 22, as in MM2(87).
[b] The charge distribution in the OAc group has been taken from MM2; the other atomic charges were calculated by the IDME procedure.
[c] Ref. 21.

field calculates that A2 is the major conformation (90%) in the gas phase (Table 6). A partial structural model (Figure 5) has been considered, since it includes most of the features characteristic of the conformational problem with this compound. The change in relative energies with the five-membered ring included in the calculations did not exceed 0·5 kcal mol^{-1}. The calculated distribution of A1, A2, B1 and B2 conformations was 16%, 80%, 0% and 4%, respectively, relative to 20%, 71% ,0% and 9% in Table 6. The difference in the MM2 dipole energies or IDME charge energies calculated without or with the five-numbered ring included is less than 0·05 kcal mol^{-1}. Treatment of all the possible conformations of the flexible side-chain would require considerable effort with only a modest gain in the quality of the results, particularly when electrostatics is concerned. Additionally, the solvation energy calculations in the IDME method are based on the reaction field theory assuming a spherical solute cavity. The shape of a partial structure model is nearly spherical, whereas the complete steroid is extended, far from the spherical shape. This makes the use of the partial structure model a simpler and also, as far as solvation is concerned, a more adequate way of treating this molecule. The three possible rotamers (gl, with $C_2{-}C_3{-}O{-}C$ angle *ca* 180 °; g2, with $C_4{-}C_3{-}O{-}C$ angle 180 °, and a, with $H{-}C_3{-}O{-}C$ angle 180 °) around the $C_3{-}O$ bond have been considered for the conformations A1, A2, B1 and B2. The calculated conformational energies (Table 6) are statistically weighted values. Figure 4 shows for each of the four conformations the most stable orientation of the AcO group in solution. These are the most stable orientations of the AcO group in the gas phase also. Only the *trans* form of the ester group was considered, since the *cis* form is more than 3 kcal mol^{-1} higher in energy.

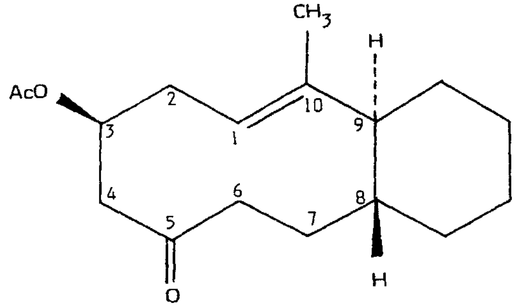

Figure 5. Partial structural model of (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one

The proportion of A2 decreased to 71% relative to A1 and B2 when the new torsional parameters[22] for carbonyl compounds were introduced. It decreased further when inductive effects were taken into account, through the charge interaction energy calculated by IDME method. Stabilization of the A1 and B2 conformations relative to the A2 conformation is due to the charge interactions, mainly to the interactions between strong C=O dipoles of the keto and ester groups whose distances and mutual orientations are particularly favorable in the A1 and B2 conformations with the $H{-}C_3{-}O{-}C$ angle *ca* 180°. The polarities of these dipoles are increased by inductive effects.

The solvation effects are responsible for further stabilizations of the A1 relative to the A2 conformation. To calculate the solvent effects we used the model of an eccentric dipole and quadrupole[23] in a spherical cavity. The effect of eccentricity is small for the small molecules[23] but its importance increases with increasing size of a molecule and is found to be the major reason for the stability of the A1 conformation in solution (Table 6) (the molecular constants such as density and

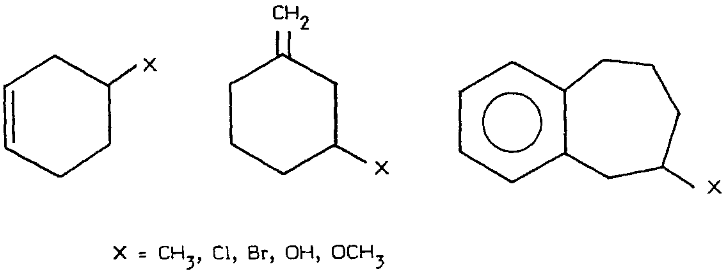

Figure 6. The three basic classes of compounds studied

refractive index are unknown for the compound in question; therefore, the radius of the molecule was calculated from the volume of the molecule obtained by the MOLSPACE[24] program). Although conformational energies in the gas phase and also the solvent effects depend mainly on the charge interactions between strongly polar groups, the charges on the hydrocarbon part of a molecule have to be considered. Without taking these charges into account, the eccentricity of the dipole and quadrupole in the A1 conformation were too large, and the stability of the A1 conformation would have been overestimated by more than 7 kcal mol^{-1}. The results obtained by the MM2–IDME method are generally similar to those obtained by the MM2 method. The $C_{sp^2}—C_{sp^2}$, $C_{sp^3}—C_{sp^2}$ and $C_{sp^2}—H$ bonds are not polar enough to make electrostatic effects dominate conformational equilibria and solvation. The other effects such as orbital interactions in the gas phase and specific interactions with solvent molecules in solution may dominate. However, in molecules that have two or more polar groups close enough to have strong interactions, the MM2–IDME method is expected to provide a better treatment of conformational effects and solvation. These expectations are borne out in the limited number of available examples.[2]

REFERENCES

1. U. Burkert and N. L. Allinger, *Molecular Mechanics*. American Chemical Society, Washington, DC (1982.
2. (a) L. Dosen-Micovic, D. Jeremic and N. L. Allinger, *J. Am. Chem. Soc.* **105**, 1716 (1983); (b) L. Dosen-Micovic, D. Jeremic and N. L. Allinger, *J. Am. Chem. Soc.* **105**, 1723 (1983).
3. R. J. LeFevre, *Adv. Phys. Org. Chem.* **92**, 2191 (1970).
4. G. Del Re, *J. Chem. Soc.* 4031 (1958).
5. A. L. McClellan, *Tables of Experimental Dipole Moments*, Vol. 1, Freeman, San Francisco (1963); Vol. 2, Rahara Enterprises (1974).
6. W. J. Hehre and J. A. Pople, *J. Am. Chem. Soc.* **92**, 2191 (1970).
7. R. J. Abraham and E. Bretschneider, in *Internal Rotation in Molecules*, edited by W. J. Orville-Thomas. Wiley, London (1974).
8. J. B. Lambert and R. R. Clikeman, *J. Am. Chem. Soc.* **98**, 4204 (1976).
9. M. St.-Jacques and D. Menard, *Tetrahedron* **39**, 1041 (1983).
10. D. E. Marko and J. B. Lambert, *J. Am. Chem. Soc.* **107**, 7978 (1985).
11. N. S. Zefirov, V. V. Samoshin and G. M. Akhmetova, *Zh. Org. Khim.* **21**, 203 (1985).
12. J. B. Lambert and K. M. Taba, *J. Am. Chem. Soc.* **103**, 5829 (1981).
13. R. Lauricella, J. Kechayan and H. Bodot, *J. Org. Chem.* **52**, 1577 (1987).
14. M. J. Cook, K. Nasri and S. M. Vather, *Tetrahedron Lett.* **27**, 3853 (1986).
15. E. L. Eliel and R. M. Enanoza, *J. Am. Chem. Soc.* **94**, 8072 (1972).
16. L. A. Gorthey, M. Vairamani and C. Djerassi, *J. Org. Chem.* **50**, 4173 (1985).
17. J. B. Lambert, L. Xue, R. J. Bosch, K. M. Taba, D. E. Marko, S. Urano and P. R. LeBreton, *J. Am. Chem. Soc.* **108**, 7575 (1986).
18. M.-L. Stien, M. Claessens, A. Lopez and J. Reisse, *J. Am. Chem. Soc.* **104**, 5902 (1982).
19. J. I. Gersten and A. M. Sapse, *J. Phys. Chem.* **85**, 3407 (1981).
20. J. P. Bowen and N. L. Allinger, *J. Org. Chem.* **52**, 1830 (1987).
21. H.-C. Mez, G. Rist, O. Ermer, L. Lorenc, J. Kalvoda and M. L. Mihailovic, *Helv. Chim. Acta* **59**, 1273 (1976).
22. J. P. Bowen, A. Pathiaseril, S. Profeta, Jr, and N. L. Allinger, *J. Org. Chem.* **52**, 5162 (1987).
23. L. Dosen-Micovic and V. Zigman, *J. Chem. Soc., Perkin Trans. 2* 625 (1985).
24. D. H. Wertz, PhD Thesis, University of Georgia (1974).
25. N. L. Allinger, *J. Am. Chem. Soc.* **99**, 8127 (1977).